

## **Abstract**

The present invention provides a method for merging combinatorial biosynthesis with techniques of synthetic organic chemistry. In general, this method, combinatorial biology, involves 1) providing "starter units", wherein the starter units are capable of being accepted by the modular biosynthetic enzymatic machinery, and have incorporated therein a "functional handle" capable of reacting with specific functionality present on a solid support; 2) feeding these "starter units" into the modular biosynthetic enzymatic machinery, *in vivo* or *in vitro*, to obtain complex template molecules; and 3) further functionalizing the complex template molecules using synthetic organic chemistry to provide a collection of complex "unnatural" natural products having structural, topological, stereochemical and functional diversity. In one preferred embodiment, the starter units are attached to solid support units prior to being exposed to the modular biosynthetic enzymatic machinery. In another preferred embodiment, the starter units are exposed to the modular biosynthetic enzymatic machinery directly and thus the templates produced by the machinery are thus attached to the solid support. The starter units and the template structures used in the method of the present invention can both be diversified using synthetic organic chemistry.

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